UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
Address: COMMISSIONER FOR PATENTS
P.O. Box 1450
Alexandria, Virginia 22313-1450
www.uspto.gov

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/781,724	02/20/2004	Jonathan Gressel	27627	4015

7590 06/12/2006

Martin D. Moynihan
PRTSI, Inc.
P. O. Box 16446
Arlington, VA 22215

EXAMINER	
PROUTY, REBECCA E	
ART UNIT	**PAPER NUMBER**
1652	

DATE MAILED: 06/12/2006

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No. 10/781,724	Applicant(s) GRESSEL ET AL.	
	Examiner Rebecca E. Prouty	Art Unit 1652	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☐ Responsive to communication(s) filed on _____.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) 48-57 is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) 48-57 is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on 20 February 2004 is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☒ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☒ Certified copies of the priority documents have been received in Application No. 09/889,738.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

Claims 1-47 and 58-83 have been canceled. Claims 48-57 are at issue and are present for examination.

Claims 48-57 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

These claims are directed to methods of use of a genus of flavanone-7-O-glucoside-2"-O-rhamnosyl-transferases or cells overexpressing a flavanone-7-O-glucoside-2"-O-rhamnosyl-transferase gene, producing activated rhamnose and capable of intake of hesperetin-7-glucoside and hesperidinases. The specification teaches the structure of only a single representative species of such flavanone-7-O-glucoside-2"-O-rhamnosyl-transferases and flavanone-7-O-glucoside-2"-O-rhamnosyl-transferase gene to be overexpressed, teaches only the species *Lactobacillus casei*, *Lactobacillus delbrueckeii*, *Saccharomyces cerevisiae*, tobacco(*Nicotiana tabacum*), grapes (*Vitis vinferis*) and carrot (*Daucus carota*), as species of cells producing activated rhamnose and capable of intake of hesperetin-7-glucoside and does not teach a single species of

hesperidinase. Moreover, the specification fails to describe any other representative species of flavanone-7-O-glucoside-2"-O-rhamnosyl-transferase by any identifying characteristics or properties other than the functionality of flavanone-7-O-glucoside-2"-O-rhamnosyl-transferase activity, the specification fails to describe any other representative species of flavanone-7-O-glucoside-2"-O-rhamnosyl-transferase gene by any identifying characteristics or properties other than the functionality of encoding a protein having flavanone-7-O-glucoside-2"-O-rhamnosyl-transferase activity, fails to describe any other representative species of host cell by any identifying characteristics or properties other than the ability to producing activated rhamnose take up hesperetin-7-glucoside and the specification fails to describe any representative species of hesperidinase by any identifying characteristics or properties other than the functionality of hesperidinase activity. Given this lack of description of representative species of flavanone-7-O-glucoside-2"-O-rhamnosyl-transferases or cells overexpressing a flavanone-7-O-glucoside-2"-O-rhamnosyl-transferase gene, producing activated rhamnose and capable of intake of hesperetin-7-glucoside and hesperidinases used in the methods of the claims, the specification fails to sufficiently describe the claimed invention in such full, clear,

concise, and exact terms that a skilled artisan would recognize that applicants were in possession of the claimed invention.

Claims 48-57 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for methods of producing neohesperidin or neohesperidin dihydrochalcone using the flavanone-7-O-glucoside-2"-O-rhamnosyl-transferase of SEQ ID NO:21 or *Lactobacillus casei*, *Lactobacillus delbrueckeii*, *Saccharomyces cerevisiae*, tobacco(*Nicotiana tabacum*), grapes (*Vitis vinferis*) and carrot (*Daucus carota*) cells transformed with a gene encoding therefore, does not reasonably provide enablement for methods of producing neohesperidin or neohesperidin dihydrochalcone using any flavanone-7-O-glucoside-2"-O-rhamnosyl-transferase or any host cell expressing any flavanone-7-O-glucoside-2"-O-rhamnosyl-transferase gene. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims.

Claims 48-57 are so broad as to encompass methods of producing neohesperidin or neohesperidin dihydrochalcone using any flavanone-7-O-glucoside-2"-O-rhamnosyl-transferase or any host cell expressing any flavanone-7-O-glucoside-2"-O-rhamnosyl-transferase gene. The scope of the claims is not commensurate

with the enablement provided by the disclosure with regard to the extremely large number of flavanone-7-O-glucoside-2″-O-rhamnosyl-transferases or flavanone-7-O-glucoside-2″-O-rhamnosyl-transferase genes and host cells therefore broadly necessary to practice the methods encompassed by the claims. Since the amino acid sequence of a protein determines its structural and functional properties, predictability of which changes can be tolerated in a protein's amino acid sequence and obtain the desired activity requires a knowledge of and guidance with regard to which amino acids in the protein's sequence, if any, are tolerant of modification and which are conserved (i.e. expectedly intolerant to modification), and detailed knowledge of the ways in which the proteins' structure relates to its function. However, in this case the disclosure is limited to a single flavanone-7-O-glucoside-2″-O-rhamnosyl-transferase and gene encoding therefore. Furthermore, the methods of claims 51, 52, 56 and 57 require use of a host cell capable of producing activated rhamnose and capable of intake of hesperetin-7-glucoside yet the specification identifies only the species *Lactobacillus casei*, *Lactobacillus delbrueckeii*, *Saccharomyces cerevisiae*, tobacco(*Nicotiana tabacum*), grapes (*Vitis vinferis*) and carrot (*Daucus carota*) as having these properties. The ability to produce a particular activated sugar nucleotide and

to take up a particular flavanone-glucoside is highly variable among different species as it is dependent on the genetic characteristics of each individual organism to produce whatever protein(s) is necessary for effecting these characteristics yet the specification provides no identification as to what other cells would have these characteristics.

While recombinant and mutagenesis techniques are known, it is not routine in the art to screen for multiple substitutions or multiple modifications, as encompassed by the instant claims, and the positions within a protein's sequence where amino acid modifications can be made with a reasonable expectation of success in obtaining the desired activity/utility are limited in any protein and the result of such modifications is unpredictable. In addition, one skilled in the art would expect any tolerance to modification for a given protein to diminish with each further and additional modification, e.g. multiple substitutions.

The specification does not support the broad scope of the claims which encompass using any flavanone-7-O-glucoside-2″-O-rhamnosyl-transferase or any host cell expressing any flavanone-7-O-glucoside-2″-O-rhamnosyl-transferase gene because the specification does **not** establish: (A) regions of the protein structure which may be modified without effecting flavanone-7-O-

glucoside-2"-O-rhamnosyl-transferase activity; (B) the general tolerance of flavanone-7-O-glucoside-2"-O-rhamnosyl-transferases to modification and extent of such tolerance; (C) a rational and predictable scheme for modifying any flavanone-7-O-glucoside-2"-O-rhamnosyl-transferase residues with an expectation of obtaining the desired biological function; (D) an identification of what cells are capable of producing activated rhamnose and taking up hesperetin-7-glucoside or how said cells can be identified and (E) the specification provides insufficient guidance as to which of the essentially infinite possible choices is likely to be successful.

Thus, applicants have not provided sufficient guidance to enable one of ordinary skill in the art to make and use the claimed invention in a manner reasonably correlated with the scope of the claims broadly including methods of producing neohesperidin or neohesperidin dihydrochalcone using any flavanone-7-O-glucoside-2"-O-rhamnosyl-transferase or any host cell expressing any flavanone-7-O-glucoside-2"-O-rhamnosyl-transferase gene. The scope of the claims must bear a reasonable correlation with the scope of enablement (In re Fisher, 166 USPQ 19 24 (CCPA 1970)). Without sufficient guidance, determination of flavanone-7-O-glucoside-2"-O-rhamnosyl-transferases or any host cells expressing a flavanone-

7-O-glucoside-2"-O-rhamnosyl-transferase gene having the desired biological characteristics for use in the claimed methods is unpredictable and the experimentation left to those skilled in the art is unnecessarily, and improperly, extensive and undue. See In re Wands 858 F.2d 731, 8 USPQ2nd 1400 (Fed. Cir, 1988).

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

Claims 48, 49, 53, and 54 are rejected under 35 U.S.C. 103(a) as being unpatentable over Horowitz et al. in view of Bar-Peled et al. and Lewinsohn et al.

Horowitz et al. teach a process for the synthesis of neohesperidin comprising hydolyzing hesperidin to remove the rhamnose residue attached at the 6 position of the glucose to produce hespertin-7-glucoside (H7G) and then using a flavanone-7-O-glucoside-2"-O-rhamnosyl-transferase of young pummelo leaves to catalyze the transfer of rhamnose from UDP-rhamnose to the 2-position of the H7G (see pages 5 and 6). Horowitz et al. further teach that the neohesperidin produced by this process

can be further used for the synthesis of neohesperidin dihydrochalcone by treating neohesperidin with alkali to obtain neohesperidin chalcone and then reducing the neohesperidin chalcone to neohesperidin dihydrochalcone (see page 2 and Figure 1).

Bar-Peled et al. teach the isolation of a flavanone-7-O-glucoside-2"-O-rhamnosyl-transferase of young pummelo leaves and methods of using this enzyme to catalyze the transfer of rhamnose from UDP-rhamnose to the 2-position of the H7G.

Lewinsohn et al. teach the preparation of H7G by the catalytic hydrolysis of hesperidin using hesperidinase (see page 2534).

Thus it would have been obvious to accomplish the process taught by Horowitz et al. for the production of neohesperidin and further use of said neohesperidin for the production of neohesperidin dihydrochalcone by using the process of Lewinsohn et al. to convert hesperidin to H7G and using the process of Bar-Peled et al. to convert the H7G to neohesperidin as Horowitz et al. teach that this process would provide for the synthesis of the sweetener neohesperidin dihydrochalcone hesperidin from hesperidin which is a widely available byproduct of the orange processing industry while current sources of this compound are much less plentiful.

Claims 50 and 55 are rejected under 35 U.S.C. 103(a) as being unpatentable over Horowitz et al. in view of Bar-Peled et al. and Lewinsohn et al. as applied to claims 48, 49, 53, and 54 above, and further in view of Krasnobajew (GB 1404306).

Horowitz et al., Bar-Peled et al. and Lewinsohn et al. are discussed above and make obvious a process of producing neohesperidin by hydolyzing hesperidin using a hesperidinase to remove the rhamnose residue attached at the 6 position of the glucose to produce hespertin-7-glucoside (H7G) and then using a flavanone-7-O-glucoside-2″-O-rhamnosyl-transferase of young pummelo leaves to catalyze the transfer of rhamnose from UDP-rhamnose to the 2-position of the H7G, and the further processing of said neohesperidin to neohesperidin dihydrochalcone. However, Horowitz et al., Bar-Peled et al. and Lewinsohn et al. do not teach the immobilization of the hesperidinase used in said process.

Krasnobajew teach the immobilization of hesperidinase to a solid support and teach that immobilizing the enzyme as taught inhibits any ß-glucosidase activity of the enzyme. As the removal of the glucose residue from H7G would destroy the substrate for the flavanone-7-O-glucoside-2″-O-rhamnosyl-transferase in the process of producing neoheperidin made obvious by Horowitz et al., Bar-Peled et al. and Lewinsohn et

al., a skilled artisan would have understood that limiting this activity in the hesperidinase would be advantageous. Therefore, it would have been obvious to one of ordinary skill in the art to use the immobilized hesperidinase of Krasnobajew in the process in order to limit the presence of ß-glucosidase activity in the hesperidinase preparation.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Rebecca E. Prouty whose telephone number is 571-272-0937. The examiner can normally be reached on Tuesday-Friday from 8 AM to 5 PM. The examiner can also be reached on alternate Mondays

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Ponnathapura Achutamurthy, can be reached at (571) 272-0928. The fax phone number for this Group is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Rebecca Prouty
Primary Examiner
Art Unit 1652